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The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood

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ABSTRACT

Very preterm children are at higher risk to develop behavioral and emotional problems, poor sleep, and altered hypothalamic-pituitary-adrenocortical activity (HPAA). However, knowledge on objective sleep and HPAA as well as their role for the development of behavioral and emotional problems in very preterm children is limited. Fifty-eight very preterm children (<32nd gestational week) and 55 full-term children aged 6–10 years underwent one night of in-home polysomnographic sleep assessment. HPAA was assessed with four saliva samples in the morning (morning cortisol secretion) and four saliva samples in the evening (evening cortisol secretion). Parents completed the Strengths and Difficulties Questionnaire (SDQ) to assess children's behavioral and emotional problems and a subscale of the Children's Sleep Habits Questionnaire to assess sleep disordered breathing. Very preterm children showed more behavioral and emotional problems (SDQ total behavioral/emotional difficulties, emotional symptoms), poorer sleep (more nocturnal awakenings, more stage 2 sleep, less slow wave sleep), and faster decreasing evening cortisol secretion compared to full-term children. Across the whole sample, more stage 2 sleep and/or less slow wave sleep were associated with more SDQ total behavioral/emotional difficulties, hyperactivity-inattention, and peer problems. Lower morning cortisol secretion and lower evening cortisol secretion were associated with more conduct problems. In very preterm children, increased SDQ total behavioral/emotional difficulties was partially explained by less restorative sleep including more stage 2 sleep and less slow wave sleep. This result points to the importance of restorative sleep for the behavioral and emotional development of very preterm children during middle childhood.

1. Introduction

Pre- and perinatal adversities shape the development of health problems throughout the life-span, including mental health disturbance (Barker et al., 2002). The present study aims at shedding light on possible pathways through which very preterm birth (<32nd gestational week) – a major perinatal adversity involving medical complications and invasive and often painful treatment procedures, which occurs in around 1% of all births in the western world (Beck et al., 2010) – may impact on mental health during childhood, namely by altering (a) sleep patterns and (b) hypothalamic–pituitary–adrenocortical activity (HPAA).

Generally healthy very preterm born children are at higher risk for lower mental health including psychosocial impairments such as more behavioral problems (e.g. attention problems) and emotional problems (e.g. emotional symptoms such as anxiety and depression) (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002) with an up to three times increased prevalence of mood disorders during childhood and adolescence (Burnett et al., 2011). One reason for decreased psychosocial adjustment of formerly preterm

Abbreviations: AUC, area-under-the-concentration-time-curve; EEG, electroencephalography; HPAA, Hypothalamic–pituitary–adrenocortical activity; PSG, Polysomnography; REM sleep, rapid eye movement sleep; SDB, sleep-disordered breathing; SDQ, Strengths and Difficulties Questionnaire; SWS, slow wave sleep.

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children includes persistent alterations in sleep regulation (Rosen et al., 2003; Lemola, in press). Particularly, sleep disordered breathing (SDB) is more prevalent in formerly very preterm children (Rosen et al., 2003).

Generally, adequate sleep is an important determinant of psychosocial adjustment in childhood. School-age children (i.e., between 6 and 11 years) have a high sleep need of around 9–11 h per night (Iglowstein et al., 2003), while sleep disturbances are common with a prevalence of around 30% (Fricke-Oerkermann et al., 2007). Importantly, a large body of evidence shows that children with disturbed sleep are at higher risk for behavioral and emotional problems (for a meta-analysis see Astill et al., 2012). Experimental studies further indicate that already modest changes in sleep duration have a causal impact on children's behavioral problems (Gruber et al., 2012). However, studies measuring sleep objectively in non-clinical samples are scarce. Particularly, research conducted in an ecological setting, i.e., at the children's home, measuring sleep objectively applying sleep-electroencephalography (EEG) to examine the relationship between sleep architecture and children's behavior problems are rare. One study applying in-home sleep-EEG in 58 healthy preschoolers showed that increased stage 2 sleep and decreased slow wave sleep (SWS, or deep sleep) were associated with more behavioral and emotional problems (Hatzinger et al., 2013). Similarly, in-home polysomnography (PSG) studies in adolescents reported that more light sleep (sleep stages 1 and 2) and less SWS was associated with subclinical depressive symptoms (Brand et al., 2010), and lower scores on personality traits associated with resilience such as mental toughness (Brand et al., 2014). Taken together, these studies applying in-home PSG in healthy children and adolescents indicate that less restorative sleep (i.e., more light sleep, less SWS) is related to poor psychosocial adjustment. In particular decreased SWS, which is considered to be the most restorative sleep stage (Borbély and Achermann, 1999), has been suggested to involve decreased energy levels for the next day and therefore increased vulnerability for psychological difficulties.

A second possible reason for decreased psychosocial adjustment of preterm children include persistent alterations of the HPAA, which may be caused by painful treatment procedures, separation from parents, and treatment with artificial glucocorticoids during the perinatal phase (Karemaker et al., 2008; Kaseva et al., 2014; Lemola, in press). A large body of evidence shows that alterations in the HPAA in childhood and adolescence are related to psychosocial impairments. Generally, a hypoactive HPAA is associated with more behavioral problems, while a hyperactive HPAA is associated with more emotional problems (Hartman et al., 2013). Research on the HPAA in preterm children is scarce, but two studies lend support to the notion that preterm children show an altered HPAA. One study with 18 preterm children aged 8-14 found a trend towards a decreased cortisol response to psychosocial stress, but an increase of morning cortisol secretion (Buske-Kirschbaum et al., 2007). Similarly, Kaseva et al. (2014) found a blunted cortisol response to psychosocial stress in young adults born preterm with very low birth weight.

Taken together, there is evidence that very preterm children are at higher risk for psychosocial impairments, poor sleep and an altered HPAA. However, there are important gaps in research. First, studies examining objectively assessed sleep using PSG in very preterm children are missing. Second, studies on the relationship between sleep architecture as assessed with in-home sleep-EEG and psychosocial adjustment are rare. Third, studies on HPAA in very preterm children during middle childhood are rare, too, and missing altogether for associations between HPAA and psychosocial adjustment. Finally and most importantly, to date no study has tested whether alterations in sleep and/or HPAA are possible mediators of the effect of preterm birth on psychosocial adjustment. The main goal of the present study was therefore to shed light on possible underlying mechanism in the association between very preterm birth and psychosocial adjustment by examining the role of sleep and HPAA. The following hypotheses were proposed. First, we hypothesized to find more behavioral and emotional problems, poorer sleep (i.e., shorter sleep duration, lower sleep efficiency, more nocturnal awakenings, more light sleep (stage 1 and/or stage 2 sleep), less SWS, more SDB) and an altered HPAA in very preterm compared to full-term children. Second, we hypothesized that poorer sleep is associated with more behavioral and emotional problems and that HPAA is negatively associated with behavioral problems and positively associated with emotional problems. Third, we hypothesized that less favorable sleep-EEG and/or altered HPAA characteristics in very preterm children account for differences in behavioral and emotional problems between very preterm and full-term children.

2. Methods

2.1. Study population

Fifty-eight healthy very preterm children (<32nd gestational week; age: $M = 8.2$ years, $SD = 1.3$; range: 6.0–10.9) and 55 full-term children (age: $M = 8.3$, $SD = 1.3$; range: 6.3–10.6) were recruited for the present study.

Fig. 1 describes the inclusion procedure of very preterm children, who were recruited from an initial cohort of 217 prematurely born children treated at the University Children's Hospital Basel (Switzerland). Participating preterm children did not differ from non-participants with regard to birth weight (1302 g vs. 1284 g, $F(1,216) = .09$; $P = .76$), gestational age (29.7 weeks vs. 29.7 weeks,

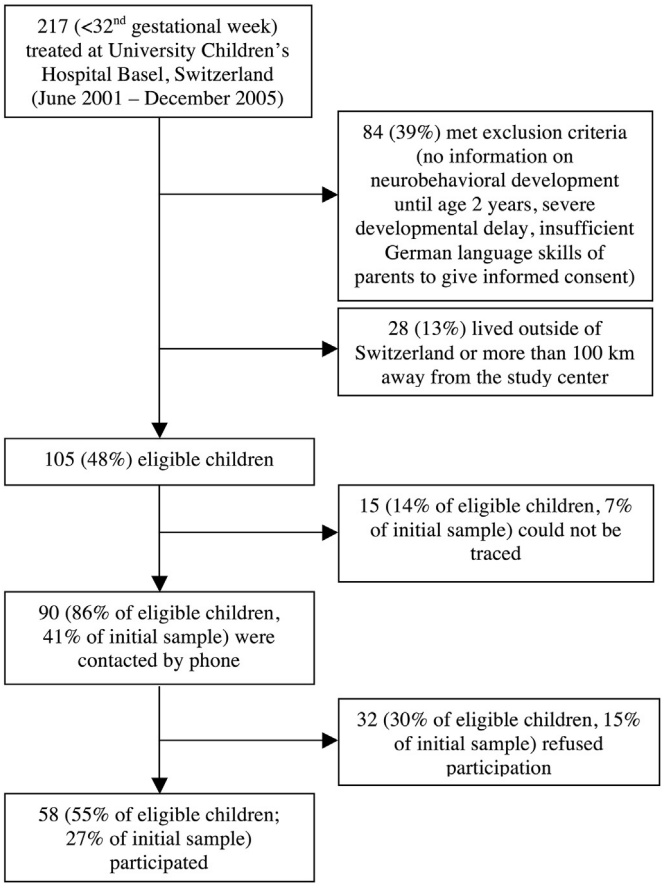

Fig. 1. Scope diagram describing the inclusion procedure of very preterm children.

$F(1,216) = .003$; $P = .96$) or length of hospital stay (53.9 days vs. 53.1 days, $F(1,180) = .05$; $P = .83$). The sample characteristics are presented in Table 1.

The full-term children (>37 weeks of gestation) were recruited from official birth notifications. The two samples were comparable regarding age and gender. All children attended primary school in Switzerland. Among the preterm children eight received additional support at school (e.g. by a remedial teacher) or visited small group classes, while none of the full-term children received any additional support.

To estimate the statistical power given the sample size of the study, post-hoc power analysis was performed with G*Power (Faul et al., 2007). Regarding mean differences between preterm and full-term children, the power analysis indicated an 84% chance of detecting effects of medium size ($d = .50$) at a .05 alpha level (one-sided). Regarding correlations between two variables the chance of detecting effects of medium size ($r = .30$) was 95% at a .05 alpha level (one-sided; based on the total sample size). The study was thus sufficiently powered to detect medium size effects (Cohen, 1988).

Parents gave written informed consent for the children to participate and assent was obtained from the child. The study was approved by the Ethics Committee of Basel and performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Procedure

Trained study personnel visited the children at home on a regular school day to complete cognitive assessments (which are not reported here), collect saliva samples, and administer in-home PSG. Parents completed questionnaires to assess demographic data, children's psychosocial impairments, and SDB. Children received gift vouchers of CHF 40 for participating (1 CHF = 1.12 USD; September 2014). Mothers and fathers received CHF 30 each for completing questionnaires, removing the PSG device, and collecting morning cortisol saliva samples. Information on neonatal health of the very preterm sample was obtained from the medical files of the University Children's Hospital Basel.

2.3. Assessment of children's behavioral and emotional problems

Psychosocial impairments were assessed with the German version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) measuring two domains of behavioral problems (conduct problems, hyperactivity-inattention) and two domains of emotional problems (emotional symptoms, peer problems) with five items each, as well as a composite score of total behavioral/emotional difficulties. The fifth domain of the SDQ assessing prosocial behavior was not included in the present study, as the study focus is on behavioral and emotional difficulties. Items were rated on a 3-point Likert scale ranging from 0 (*not true*) to 2 (*certainly true*). Higher subscale scores reflect more difficulties. Cronbach's alpha for total behavioral/emotional difficulties was $\alpha = .64$ for mothers and $\alpha = .74$ for fathers. As an index of interrater agreement intra-class correlations (ICC) were calculated for mother- and father-reports. The agreement for total behavioral/emotional difficulties was high ($ICC = .67$, $P < .001$). Cronbach's alpha for emotional symptoms was $\alpha = .66$ (mothers), $\alpha = .77$ (fathers; $ICC = .52$, $P < .001$), for conduct problems $\alpha = .47$ (mothers), $\alpha = .48$ (fathers; $ICC = .58$, $P < .001$), for hyperactivity-inattention $\alpha = .81$ (mothers), $\alpha = .80$ (fathers; $ICC = .72$, $P < .001$), and for peer problems $\alpha = .53$ (mothers), $\alpha = .46$ (fathers; $ICC = .62$, $P < .001$). As intra-class correlations for mother and father reports were high (ranging between .52 and .72) and to increase reliability, mother and father ratings were combined. Mother questionnaires were available for 109 children, father questionnaires were available for 92 children, and for 4 children, no parent questionnaires were available. For 17 children no father ratings were available while they had mother ratings, so only the mother ratings were used.

Table 1
Sample characteristics of very preterm and full-term children.

	Very preterm ($n = 58$)		Full-term ($n = 55$)		*P*
	M/N	(SD/%)	*M/N*	(SD/%)	
Age, years	8.2	(1.3)	8.3	(1.3)	.53
Sex, male	40	(69.0)	35	(63.6)	.55
Gestational age, weeks	29.7	(1.9)	39.7	(1.6)	<.001
Birth weight, grams	1302.1	(408.3)	3338.4	(441.3)	<.001
Prenatal treatment with glucocorticoids	40	(69.0)	0	(0)	<.001
Postnatal treatment with glucocorticoids	4	(6.9)	0	(0)	.12
Infant respiratory distress syndrome	45	(77.6)	0	(0)	<.001
Apnea of Prematurity	46	(79.3)	0	(0)	<.001
Bronchopulmonary Dysplasia	3	(5.2)	0	(0)	.24
First language (German)	38	(65.5)	46	(83.6)	.03
Maternal education					<.001
No vocational training	9	(15.5)	3	(5.5)	
Vocational education	41	(70.7)	25	(45.5)	
University	8	(13.8)	27	(49.1)	

Note. *P*-values of the χ^2 test, Fisher's exact test, or analyses of variance.

2.4. Sleep assessment

Sleep was assessed using in-home PSG during the night following the home-visit. Polysomnogram signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained using the Compumedics Somté PSG. Sleep polygraphs were visually analyzed by two experienced raters according to the standard procedures (Rechtschaffen and Kales, 1968). Parents completed a short sleep log for the night of assessment and reported on children's exact awakening time to determine the end of sleep scoring. The following sleep parameters were derived: Sleep continuity: Total sleep time (time in bed minus time spent awake in hours), sleep efficiency (total sleep time/time in bed × 100), and nocturnal awakenings (number of arousals from sleep). Sleep architecture (min): Stages 1, 2, SWS (slow wave sleep: stages 3 and 4), REM sleep, and REM latency. Polysomnographic sleep data was available for 52 (89.7%) very preterm and 50 (90.9%) full-term children.

To assess SDB, parents completed the SDB subscale of the Children's Sleep Habits Questionnaire (CSHQ; Owens et al., 2000) including three items on snoring and breathing problems in children rated on a 3-point Likert scale ranging from 0 (*rarely*) to 2 (*usually*). Mother and father ratings were combined to increase reliability. Cronbach's alpha was $\alpha = .84$ for mothers and $\alpha = .85$ for fathers. Agreement between mothers and fathers was very high ($ICC = .88$, $P < 0.001$).

2.5. HPAA assessment

2.5.1. HPA activity

HPAA was assessed by saliva cortisol samples collected during the home-visit in the evening before and in the morning after PSG assessment. Morning cortisol secretion: In the morning after PSG assessment, parents collected four saliva samples at 0, 10, 20, and 30 min after the child's awakening. Parents were instructed that the children were not allowed to eat or drink before collecting saliva samples. The children were asked to brush their teeth after saliva sampling was completed. Awakening times ranged from 5:20 a.m.

to 8:33 a.m. (M = 06:45 a.m., SD = 28 min) and did not differ between very preterm (M = 06:42 a.m.) and full-term children (M = 06:48 a.m.; $F(1, 101) = 1.3$, $P = 0.26$). Evening cortisol secretion: Trained study personnel collected four saliva samples at 0, 30, 60, and 90 min after the beginning of the home-visit. Children were asked not to eat or drink before collecting saliva samples. Home-visits started between 1:00 p.m. and 6:45 p.m. (M = 05:01 p.m., SD = 44 min). Average starting times did not differ between very preterm (04:58 p.m.) and full-term children (05:05 p.m.; $F(1, 108) = 0.75$, $P = 0.39$). Morning cortisol secretion is available for 54 (93.1%) very preterm and 48 (87.3%) full-term children and evening cortisol secretion is available for 55 (94.8%) very preterm and 52 (94.5%) full-term children.

2.5.2. Saliva cortisol sampling technique and cortisol analysis

Saliva samples were collected using the "Salivette" device (Sarstedt, Nümbrecht/Germany). Children were instructed to gently chew on a cotton swab for approximately 1 min and then transfer it into the small plastic tube. Free salivary cortisol concentrations were analyzed using a time-resolved immunoassay with fluorometric detection "Coat-A-Count" Cortisol RIA from DPC (Diagnostics Products Corporation; obtained through H. Biermann GmbH, Bad Nauheim, Germany).

2.6. Statistical analysis

All analyses were controlled for first language, maternal education, children's age, and gender, if not stated otherwise. We performed analysis of covariance (ANCOVA) to compare behavioral and emotional problems and sleep variables of very preterm and full-term children. Effect sizes were calculated following Cohen (1988) with $d = 0.20$ indicating small, $d = 0.50$ indicating medium, and $d = 0.80$ indicating large effect sizes. Slopes of morning and evening cortisol secretion of very preterm and full-term children were compared using repeated-measures ANCOVA to assess between-subjects effects (very preterm vs. full-term) and group × time interaction effects. Analyses involving evening cortisol were additionally controlled for the clock time of saliva sampling.

To test the association of sleep and HPAA with behavioral and emotional problems hierarchical regression analyses were performed, additionally controlling for prematurity status and for evening cortisol analyses for the clock time of saliva sampling. For these hierarchical regression analyses the area-under-the-concentration-time-curve (AUC) of cortisol secretion was calculated with the AUCg referring to the area under the curve with respect to the ground and the AUCi referring to the area under the curve with respect to the increase (Pruessner et al., 2003). Cortisol values were log-transformed before building these features as distributions of cortisol concentrations were skewed.

Finally, it was assessed whether differences in sleep and/or HPAA characteristics accounted for significant differences in behavioral and emotional problems between very preterm and full-term children applying mediation analysis according to Baron and Kenny (1986). The mediation analysis was conducted by taking only sleep and/or HPAA characteristics into account that fulfilled the preconditions for mediation based on the preceding analyses (Baron and Kenny, 1986): (1) The sleep and/or HPAA indices (the mediator) had to be significantly related to prematurity status (the independent variable) and (2) the sleep and/or HPAA indices (the mediator) had to be significantly related to behavioral and emotional problems (the dependent variable). For hypotheses involving directional predictions the reported p-values are one-tailed. All statistical computations were performed with IBM® SPSS® Statistics 20 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Differences in behavioral and emotional problems, sleep, and HPAA between very preterm and full-term children

Table 2 shows the results of the ANCOVAs comparing behavioral and emotional problems and sleep of very preterm and full-term children. Very preterm children showed more SDQ total behavioral/emotional difficulties ($F(1,102) = 3.99$, $P = .02$) and emotional symptoms ($F(1,102) = 4.89$, $P = .01$), as well as more nocturnal awakenings ($F(1,95) = 3.65$, $P = .03$), stage 2 sleep ($F(1,95) = 3.94$, $P = .03$), and less SWS ($F(1,95) = 4.01$, $P = .02$) than full-term children. There were no mean differences in conduct problems, hyperactivity-inattention, and peer problems nor in total sleep time, sleep efficiency, stage 1 sleep, REM sleep, REM latency, and SDB between very preterm and full-term children.

Cortisol secretion in the morning increased in 82 (80.4%) children across the first 30 min after awakening indicating a cortisol awakening response in the majority of the children with no differences between very preterm and full-term children (very preterm: $n = 43$; full-term: $n = 39$; $\chi^2(1) = .4$, $P = 0.83$). A repeated-measures ANCOVA showed no main effect of preterm status on morning cortisol secretion ($F(1,95) = 0.39$; $P = .54$) and no group × time interaction effect in the morning cortisol secretion ($F(1,95) = 0.65$; $P = .42$) as well as no mean differences at any time point. In the evening, cortisol secretion declined in both groups. A repeated-measures ANCOVA showed that this decline was faster among very preterm compared to full-term children with a significant group × time interaction effect ($F(1,99) = 4.99$; $P = .03$). The repeated-measures ANCOVA further indicated lower overall evening cortisol secretion of very preterm compared to full-term children ($F(1,99) = 4.05$; $P = .047$). Means of evening cortisol secretion differed at 60 min ($F(1,101) = 4.05$; $P = .047$) and at 90 min ($F(1,99) = 7.97$; $P = .006$) after the beginning of the home-visit.

3.2. Association of sleep and HPAA with behavioral and emotional problems

Table 3 shows hierarchical regression analyses for the association of sleep and HPAA with behavioral and emotional problems.

Table 2
Behavioral and emotional problems and sleep in very preterm and full-term children.

	Very preterm		Full-term		d[a]	P[a]
	M	(SD)	M	(SD)		
Behavioral and emotional problems (SDQ)						
Total behavioral/emotional difficulties	8.7	(4.4)	6.3	(4.6)	0.40	.02
Emotional symptoms	1.9	(1.7)	1.1	(1.3)	0.44	.01
Conduct problems	2.0	(1.3)	1.5	(1.3)	0.30	.07
Hyperactivity-inattention	3.4	(1.8)	2.6	(2.3)	0.28	.08
Peer problems	1.4	(1.3)	1.1	(1.2)	0.12	.28
Sleep variables						
Total sleep time, h	9.5	(0.7)	9.5	(0.6)	0.16	.23
Sleep efficiency	94.4	(2.4)	94.6	(2.7)	0.11	.29
Nocturnal awakenings	19.6	(5.9)	15.5	(7.8)	0.40	.03
Stage 1 sleep (min)	18.5	(9.9)	17.7	(14.8)	0.14	.26
Stage 2 sleep (min)	263.2	(41.8)	248.4	(35.9)	0.41	.03
Slow wave sleep (min)	139.6	(32.0)	150.0	(31.3)	0.42	.02
REM sleep (min)	145.7	(26.1)	149.3	(28.2)	0.31	.14
REM latency (min)	115.3	(47.0)	119.8	(42.2)	0.10	.65
Breathing problems (parent rating)	0.7	(1.5)	0.3	(0.5)	0.34	.10

Note.
SDQ = Strengths and Difficulties Questionnaire.
[a] Cohen's d, P-values: adjusted for first language, maternal education, children's age, and gender.

Table 3
Multiple regression with sleep and HPAA predicting behavioral and emotional problems assessed using the Strengths and Difficulties Questionnaire (SDQ).

	Total behavioral/emotional difficulties	Emotional symptoms	Conduct problems	Hyper-activity-inattention	Peer problems
Sleep variables					
Total sleep time, h	.06	.06	.09	.10	−.12
Sleep efficiency	.12	.04	.03	.13	.14
Nocturnal awakenings	.02	.12	.05	−.03	−.09
Stage 1 sleep (min)	−.02	.02	−.03	−.03	−.02
Stage 2 sleep (min)	.21*	.16	.15	.23*	.01
Slow wave sleep (min)	−.19*	−.12	−.12	−.12	−.20*
REM sleep (min)	.04	−.02	.09	−.03	.09
REM latency (min)	−.09	−.06	−.09	.02	−.16
Breathing problems (parent rating)	.10	.04	.18*	.04	.08
Morning cortisol secretion					
AUCg	.05	.13	−.03	−.02	.06
AUCi	−.08	.05	−.27**	−.06	.00
Evening cortisol secretion					
AUCg	−.10	.00	−.21*	−.12	.05
AUCi	−.01	.05	−.01	.00	−.08

Note. Data are standardized regression coefficients. All values adjusted for first language, maternal education, children's age, gender, prematurity status, and in analyses involving evening cortisol levels the clock time of saliva sampling was additionally controlled. AUCg = area-under-the-concentration-time-curve with respect to the ground; AUCi = area-under-the-concentration-time-curve with respect to the increase. *$p < 0.05$, **$p < 0.01$ (one-tailed).

More stage 2 sleep was associated with more SDQ total behavioral/emotional difficulties ($t = 2.09$, $\beta = .21$, $P = .02$) and more hyperactivity-inattention ($t = 2.28$, $\beta = .23$, $P = .01$). Less SWS was related to more SDQ total behavioral/emotional difficulties ($t = -1.88$, $\beta = -.19$, $P = .03$) and more peer problems ($t = -1.88$, $\beta = -.20$, $P = .03$). SDB was related to more conduct problems ($t = 1.80$, $\beta = .18$, $P = .04$). Total sleep time, sleep efficiency, nocturnal awakenings, stage 1 sleep, REM sleep, and REM latency were not related to behavioral and emotional problems. Lower morning cortisol secretion AUCi and lower evening cortisol secretion AUCg were associated with more conduct problems ($t = -2.81$, $\beta = -.27$, $P = .003$; $t = -2.11$, $\beta = -.21$, $P = .02$, respectively).

3.3. Mediation of the relationship between prematurity status and behavioral and emotional problems by sleep and/or HPAA

Additionally, it was tested whether differences in sleep and/or HPAA characteristics accounted for the significant differences in behavioral and emotional problems between very preterm and full-term children. Based on the previous analyses, the preconditions for mediation were met by the amount of stage 2 sleep (which was positively associated with prematurity status and SDQ total behavioral/emotional difficulties) and amount of SWS (which was negatively associated with prematurity status and SDQ total behavioral/emotional difficulties). As indices of SWS and stage 2 sleep were negatively related to each other ($r = -.42$, $P < 0.001$) and as they were differentially related to SDQ total behavioral/emotional difficulties, the mediation analysis was conducted with the ratio between deep sleep (SWS) and light sleep (stages 1 and 2 together) as the mediator. The deep sleep to light sleep ratio represents an aggregate index of a favorable sleep-EEG pattern with higher values reflecting more restorative deep sleep compared to light sleep. The mediation analysis is displayed in Fig. 2. The ratio between deep sleep and light sleep partially mediated the relationship between prematurity status and SDQ total behavioral/emotional difficulties. When the mediator (deep sleep to light sleep ratio) was entered to the regression the effect of prematurity status on SDQ total behavioral/emotional difficulties dropped from $\beta = .20$; $t = 1.96$; $p = 0.03$ ($\Delta r^2 = .032$) to $\beta = .15$; $t = 1.42$; $p = 0.08$ ($\Delta r^2 = .018$).

4. Discussion

The aim of the present study was to shed light on underlying mechanism in the association between very preterm birth and psychosocial adjustment by examining the role of sleep and HPAA. The key finding of the study is that healthy school-aged very preterm children show less restorative sleep (more stage 2 sleep and less SWS) compared to full-term children and that less restorative sleep is related to more behavioral and emotional problems which partially accounts for the difference between very preterm and full-term children in behavioral and emotional problems.

4.1. Differences in behavioral and emotional problems, sleep, and HPAA between very preterm and full-term children

First we hypothesized to find more behavioral and emotional problems, poorer sleep and an altered HPAA in very preterm compared to full-term children, which was partially supported by the data. We found that very preterm children had more total behavioral and emotional difficulties and emotional symptoms compared to full-term children which is consistent with previous research showing more internalizing behavior problems in very preterm compared to full-term children (Aarnoudse-Moens et al., 2009; Burnett et al., 2011). In contrast to previous research (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002) we found no differences in hyperactivity and inattention symptoms between very preterm and full-term children, which may be due to limited statistical power to detect modest effects (the effect size for the difference regarding hyperactivity-inattention was $d = .28$).

Regarding sleep, results are consistent with the hypothesis that very preterm children show poorer sleep involving more nocturnal awakenings, more stage 2 sleep, and less SWS compared to full-term children. Our study did not replicate the finding that very preterm children show more SDB. In our study, SDB was rated by the parents, while e.g. in the study by Rosen et al. (2003) respiratory events were measured objectively. Though speculative, it is possible that PSG derived higher levels of stage 2 sleep, more nocturnal awakenings, and lower levels of SWS in our study are a reflection of breathing problems in the very preterm children, which were not detected by the parents. As a limitation to our study, we do not have objective measures of SDB. However, the present study expands upon previous research by showing that very preterm children show less restorative sleep objectively assessed using in-home PSG.

Our expectation to find altered HPAA in very preterm compared to full-term children was supported in that very preterm children showed a faster decline in evening cortisol compared to full-term children, which is in line with reports of a hypoactive HPAA in

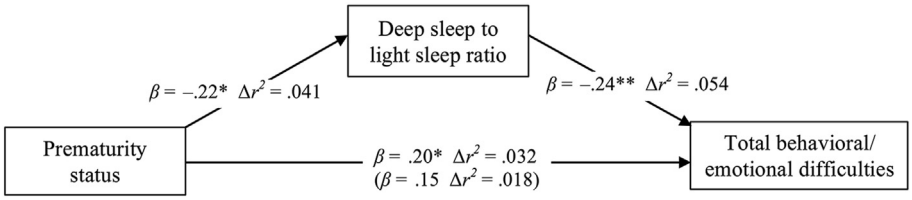

Fig. 2. Mediation of the relationship between prematurity status and behavioral/emotional difficulties by the deep sleep to light sleep ratio. Standardized regression coefficients are displayed. Prematurity status is coded 1 = very preterm birth and 0 = born at term. All analyses additionally control first language, maternal education, children's age, and gender. $^{*}p < 0.05$, $^{**}p < 0.01$ (one-tailed).

response to stress in very preterm born young adults (Kaseva et al., 2014). The faster decline in diurnal cortisol in very preterm children may be a sign of down-regulation of the HPAA due to excess exposure to glucocorticoids during the premature phase (cf. Karemaker et al., 2008). In line with Bäumler and colleagues (2013), the majority of the children in our study showed a marked increase in cortisol secretion upon awakening. However, the morning cortisol secretion did not differ between very preterm and full-term children, which is in contrast to results from Buske-Kirschbaum et al. (2007), who found an elevated cortisol awakening response in preterm children. In contrast to our study, Buske-Kirschbaum and colleagues studied older children (mean age of 10.5 years) who were born with gestational ages up to 36 weeks, which may explain differences in the findings.

4.2. Association of sleep indices and HPAA with behavioral and emotional problems

Second, we hypothesized that poor sleep and an altered HPAA are associated with more behavioral and emotional problems. The data supported this assumption in that poor sleep involving more stage 2 sleep and less SWS was associated with more total behavioral and emotional difficulties, more hyperactivity and inattention symptoms, as well as more peer problems, respectively. This is consistent with other PSG-studies reporting that alterations in objective sleep are associated with more behavioral and emotional problems in preschoolers and adolescents (Brand et al., 2010, 2014; Hatzinger et al., 2013). Importantly and beyond what was known from previous research, the present study also indicates that differences in stage 2 sleep and SWS between preterm and full-term children (as represented by the ratio between deep sleep and light sleep) may partially account for increased behavioral and emotional problems in very preterm children.

Regarding HPAA, we found that lower levels of evening cortisol secretion AUCg and a blunted morning cortisol secretion AUCi is related to conduct problems, which is in line with previous research showing that a hypoactive HPAA is associated with more behavioral problems (Hartman et al., 2013). However and in contrast to our hypothesis we found no associations of cortisol secretion and emotional problems. This finding reflects research indicating that the size of the association between cortisol secretion and emotional problems may be rather modest (Dietrich et al., 2013).

4.3. Limitations

We think our study has four limitations. First, due to the correlative design of the study, no conclusions on causal relations among the studied variables may be drawn. Second, sleep and HPAA were only assessed on a single night and day, which may reduce reliability of sleep and HPAA variables. However, sleep assessment was conducted at the children's home in familiar surroundings which we consider as an advantage compared to laboratory PSG as it improves the ecological validity of the sleep assessment (Frölich and Lehmkuhl, 2004). Third, we did not assess HPAA in response to a standardized psychosocial stressor, which would have shed further light on the HPAA of very preterm and full-term children. We did assess evening cortisol levels during assessment of cognitive functions during a home-visit, which may have been a minor social stressor for some of the children. Overall, the cognitive testing situation appeared not to have been stressful for the children as on average the cortisol levels declined steadily over the course of 90 min of testing. Last, while the current study was sufficiently powered to detect medium size effects, the statistical power was insufficient to detect small size effects.

5. Conclusions

The present study indicates that very preterm children remain at higher risk for behavioral and emotional problems as well as poor sleep during middle childhood. Poor sleep partially accounts for the increases in behavioral and emotional problems in very preterm children. Thus, it is possible that perinatal adversities related to very preterm birth affect behavioral and emotional development by altering sleep patterns. Moreover, very preterm children show a faster decline in evening cortisol levels, which may indicate a hypoactive HPAA. The present study points to the importance of sleep in very preterm born children. Clinicians who are concerned with behavioral and emotional problems of very preterm born children during middle childhood may put greater emphasis on good sleep quality.

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Contributors

NPG, PHvA, SB, EHT, AG, PW, and SL contributed to the conception and design of the study and all of them managed the literature searches and analyses. NPG collected a large subset of the data, undertook the statistical analysis and prepared and revised the manuscript. PW contributed in the acquisition interpretation of data and revised the manuscript. PHvA, SB, EHT, and AG, contributed in the interpretation of data and revised the manuscript. SL, as the principal investigator, obtained funding and supervised all stages of the study, participated in the acquisition and interpretation of data, contributed to the drafting of the manuscript, revised

the manuscript, and approved the final manuscript as submitted. All authors contributed to and have approved the final manuscript.

Conflict of interests

The authors declare no conflicts of interest.

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References

Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatr 2009;124:717–28.
Astill RG, Van der Heijden KB, Van IJzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol Bull 2012;138:1109–38.
Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. Intern J Epidem 2002;31:1235–9.
Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173–82.
Bäumler D, Kirschbaum C, Kliegel M, Alexander N, Stalder T. The cortisol awakening response in toddlers and young children. Psychoneuroendocrinology 2013;38:2485–92.
Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010;88:31–8.
Borbély AA, Achermann P. Sleep homeostasis and models of sleep regulation. J Biolog Rhythm 1999;14:559–70.
Brand S, Gerber M, Beck J, Hatzinger M, Pühse U, Holsboer-Trachsler E. Exercising, sleep-EEG patterns, and psychological functioning are related among adolescents. World J Biol Psychiatry 2010;11:129–40.
Brand S, Gerber M, Kalak N, Kirov R, Lemola S, Clough PJ, et al. Adolescents with greater mental toughness show higher sleep efficiency, more deep sleep and fewer awakenings after sleep onset. J Adolesc Health 2014;54:109–13.
Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. J Am Med Assoc. 2002;288:728–37.
Burnett AC, Anderson PJ, Cheong J, Doyle LW, Davey CG, Wood SJ. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. Psychol Med 2011;41:2463–74.
Buske-Kirschbaum A, Krieger S, Wilkes C, Rauh W, Weiss S, Hellhammer DH. Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. J Clin Endocrinol Metab 2007;92:3429–35.
Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
Dietrich A, Ormel J, Buitelaar JK, Verhulst FC, Hoekstra PJ, Hartman CA. Cortisol in the morning and dimensions of anxiety, depression, and aggression in children from a general population and clinic-referred cohort: an integrated analysis. The TRAILS study. Psychoneuroendocrinol 2013;38:1281–98.
Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.
Fricke-Oerkermann L, Plück J, Schredl M, Heinz K, Mitschke A, Wiater A, et al. Prevalence and course of sleep problems in childhood. Sleep 2007;30:1371–7.
Frölich J, Lehmkuhl G. Home polysomnography in Children–a complementary assessment method of sleep disorders in children. Somnologie 2004;8:61–4.
Goodman R. The strengths and difficulties Questionnaire: a research note. JChild Psychol Psychiatry 1997;38:581–6.
Gruber R, Cassoff J, Frenette S, Wiebe S, Carrier J. Impact of sleep extension and restriction on children's emotional lability and impulsivity. Pediatr 2012;130:1155–61.
Hartman CA, Hermanns VW, de Jong PJ, Ormel J. Self-or parent report of (co-occurring) internalizing and externalizing problems, and basal or reactivity measures of HPA-axis functioning: a systematic evaluation of the internalizing-hyperresponsivity versus externalizing-hyporesponsivity HPA-axis hypothesis. Biol Psychol 2013;94:175–84.
Hatzinger M, Brand S, Perren S, Von Wyl A, Stadelmann S, von Klitzing K, et al. In pre-school children, sleep objectively assessed via sleep-EEGs remains stable over 12 months and is related to psychological functioning, but not to cortisol secretion. J Psychiatr Res. 2013;47:1809–14.
Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatr 2003;111:302–7.
Karemaker R, Kavelaars A, ter Wolbeek M, Tersteeg-Kamperman M, Baerts W, Veen S, et al. Neonatal dexamethasone treatment for chronic lung disease of prematurity alters the hypothalamus-pituitary-adrenal axis and immune system activity at school age. Pediatr 2008;121:870–8.
Kaseva N, Wehkalampi K, Pyhälä R, Moltchanova E, Feldt K, Pesonen AK. Blunted hypothalamic-pituitary-adrenal axis and insulin response to psychosocial stress in young adults born preterm at very low birth weight. Clin Endocrinol 2014;80:101–6.
Lemola S. Long-term outcomes of very preterm birth: mechanisms and interventions. Eur Psychol 2014. in press.
Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1043–52.
Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinol 2003;28:916–31.
Rechtschaffen A, Kales A. A manual for standardized terminology, techniques and scoring system for sleep stages of human subjects. In: Brain Information Service. Los Angeles: Brain Research Institute; 1968. NIH Publ No. 204.
Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA. Prevalence and risk factors for sleep-disordered breathing in 8-to 11-year-old children: association with race and prematurity. J Pediatr 2003;142:383–9.